## Remarks

Claims 1, 4, 8-11, 31, 35, 36, 42, 43, 49, 55, 59, and 64 are pending in the application. Applicant would like to thank the Examiner for pointing out the omission of Claim 36 as a pending claim in the previous amendment.

### *§112 Rejections*

*I. Claims 1, 4, 8-11, 31, 35, 36, 42, 43, 49, 55, 59, and 64 were rejected under USC §112, first paragraph for non-enablement over the scope of the claims.*

Examiner asserts that her reference to SR141716A was used as an example to show the unpredictability in the art. This is totally erroneous. The fact that several research efforts were initiated due to the teachings of SR141716A proves that those of skill in the art had sufficient confidence in the mechanism based on these teachings to invest in their own research. In fact, SR141716A served as a benchmark for those research efforts. Although several additional references existed at the time, the two references of record referred to below clearly provided evidence of the level of knowledge in the art at the time of filing the present patent application.

Colombo, G., et al., "***Appetite Suppression and Weight Loss after the Cannabinoid Antagonist SR141716***," Life Sci, 63, PL113-PL117 (***1998***); and

Pertwee, R.G., "Pharmacology of Cannabinoid Receptor Ligands" Curr Med Chem, 6, 635-664 (***1999***). - emphasis added

Both of these articles were in the public domain prior to the time of the present invention and clearly establish that CB-1 antagonists (or inverse agonists) were known to be useful as anti-obesity agents, as well as other indications.

Examiner goes on to quote *In re Fouche* and asserts that "There are no tests done only some description of assays". Applicant would like to point out to the Examiner page 59, lines 28-29 of the specification, which clearly states "CB-1 binding activities of 4 nM and 2 nM were observed for Examples 1A-2 and 1A-3, respectively. Although the $R^4$ in both of these compounds are alkyl groups, it is important to note that it is unnecessary for an applicant to satisfy the "how-to-use" requirement of 35 USC § 112 for each member of a claimed group of compounds.

> "Early filing of an application with its disclosure of novel compounds which possess significant therapeutic use is to be encouraged. Requiring specific testing of the thousands of ... analogs encompassed by the present claim in order to satisfy the now-to-use requirement of §112 would delay disclosure and frustrate, rather than further, the interests of the public." *In re Bundy*, 209 USPQ 48, 52 (CCPA 1981).

Clearly, the binding data referred to above indicates that the compounds according to the invention are active. Even without data, however, the instant patent application, including any statement of utilities, must be taken as presumptively accurate. See in re Marzocchi, 169 USPQ 367, 369 (CCPA 1971), where it was stated:

> ""[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

The burden is on the Examiner to come forth with evidence to establish a *prima facie* case. No specific factual evidence has been presented to establish a *prima facie* case pertaining to §112 which is relevant to the present invention. Instead, Examiner states the following:

> "Another example is that of fluphenazine an approved drug for the treatment of psychotic disorders, which binds to the 5-HT6 receptor. LSD also binds the 5-HT6 receptor. According to applicants reasoning LSD should be used to treat psychotics."

Clearly, the Examiner doesn't understand the difference between an agonist and an antagonist. If a compound binds to a receptor, it has some utility if it mediates the activity of that receptor in some way (e.g., an agonist or an antagonist). However, just because a compound binds to a receptor does not indicate that all compounds that bind have the same utility. Clearly, if a compound acts as an agonist, it would not have the same properties as an antagonist. Consequently, Examiner's assertion above is ridiculous. Applicants used a known CB-1 antagonist (SR141716A) as a competitive test compound, thus Applicants have a reasonable expectation that the inventive compounds tested would have similar properties.

The Examiner bears the burden of producing sufficient evidence that one of ordinary skill in the art would have reason to doubt the claimed utility of the invention. In the instant application, it is respectfully submitted that the Examiner has not overcome that burden, i.e., she has failed to supply any credible evidence that would cause one to reasonably doubt the utility of Applicant's invention. Applicants have not cited any incredible or unbelievable utilities in their specification or claims which could be questioned by the Examiner. The multitude of references cited in the IDS's of record clearly establish that compounds that bind to the CB-1 receptor have a variety of utilities.

SR141716 is known to act as both an antagonist and inverse agonist at the CB-1 receptor and is often referred to as a CB-1 antagonist/inverse agonist. Applicant can rely on the fact that SR141716 was known to act as a CB-1 antagonist/inverse agonist with its associated

uses as a reasonable basis for utility of their compounds as tested in similar assays (e.g., competitive antagonist assay). Examiner has provided no credible evidence to the contrary. Numerous authors have discussed the uses of CB-1 antagonists as anti-obesity agents as well as other indications in the literature. See the numerous references cited in the previous IDS forms of record. As stated in MPEP 2107.03,

> "The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use. An applicant can establish a reasonable correlation by relying on statistically relevant data documenting the activity of a compound or composition, arguments or reasoning, documentary evidence (e.g., articles in scientific journals), or any combination thereof.

The MPEP also states that data generated using *in vitro* assays almost invariably will be sufficient to establish therapeutic or pharmacological utility for the compound, composition or process. Applicants respectfully submit that he has provided a reasonable correlation based on the numerous articles submitted in the IDS forms of record and the binding data submitted in the specification. Examiner has failed to provide any credible evidence contradicting this reasonable correlation.

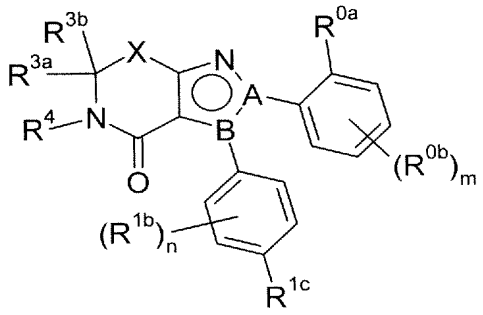
Examiner has admitted on the record that the specification is enabling for compounds wherein $R^1$ and $R^0$ are aryl(phenyl) with halogen or methoxy substituents, or $R^4$ is an alkyl, halogen substituted alkyl or a cycloalkyl, which basically represents only those compound exemplified in the specification. However, Examiner is refusing to allow a reasonable genus surrounding the exemplified compounds which is contrary to established law. As part of the enablement requirement, it is well-established that one does not have to provide exemplification of every compound that falls within the scope of the claims. Clearly, it is well within the skill of the art to make compounds as presented claimed. Examiner has failed to provide any credible evidence to the contrary. In addition, as discussed above, Examiner has failed to provide any credible evidence to refute Applicant's reasonable correlation of utility for the presently claimed compounds.

***Obviousness-Type Double Patenting Rejections***

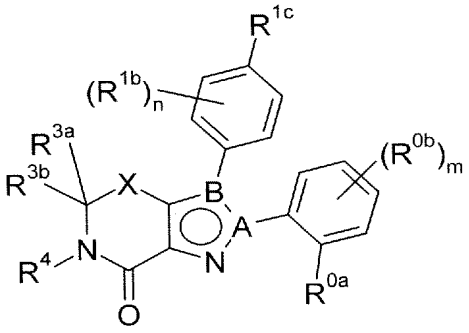
*I. Claims 1, 4, 8-11, 31, 35, 42, 43, 49, 55, 59, and 64 were rejected on the ground of nonstatutory obviousness-type double patenting over Claims 1-23 of US Patent No. 7,230,024.*

Examiner asserts that "the order is the same just the attachment is in the anticlockwise, instead of the clockwise, making them positional isomer." According to The Vocabulary of

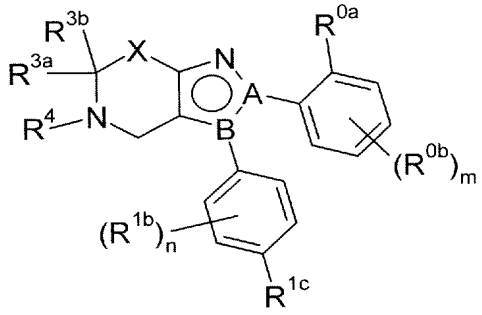
Organic Chemistry, John Wiley & Sons, Inc., Chapter 5, pg 120 (1980), "5.050 Positional Isomers Structural isomers that differ only with respect to the point of attachment of a substituent." For example, 1-Chloropropane and 2-chloropropane. See attached Appendix. Although the structures below would be considered structural isomers, they are not positional isomers. Clearly, changing the orientation of the core is much more than just moving the "point of attachment of a substituent." If one compares the two Formula (III) structures below, one can easily see that access to the carbonyl is hindered in one of the structures but not in the other one. In both the Formula (III) and Formula (IV) structures, the closeness of the $R^{3a}$ and $R^{3b}$ substitutents on one orientation would have more influence on the phenyl group than the other orientation. This could easily effect the binding of the compound to a receptor.



(III)

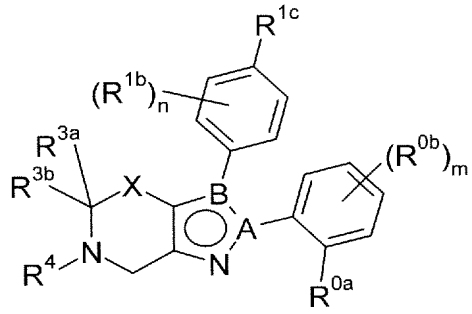


**(III)**



(IV)

*Compounds of the present invention*



**(IV)**

*Compounds of US 7,230,024*

In all of the compounds above, X is a bond, A is nitrogen and B is carbon.

It is well known that binding to a receptor can be influenced by the orientation of the groups on the compound; consequently, one would not be able to predict with any certainty that such a compound would work until it was made and tested. Therefore, it would not be obvious that the

compounds of the present invention would even bind to the CB-1 receptor let alone act as a CB-1 antagonist/inverse agonist based on the compounds disclosed and claimed in US 7,230,024.

Applicants respectfully submit that the independent claims and the claims dependent thereon are in condition for allowance.

Respectfully Submitted:

Date: August 14, 2008

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## APPENDIX

# The Vocabulary of Organic Chemistry

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*Examples.* Ethanol ($CH_3CH_2OH$) and dimethyl ether ($CH_3OCH_3$) are structural isomers.

**5.040 Constitutional Isomers**
Synonymous with structural isomers.

**5.050 Positional Isomers**
Structural isomers that differ only with respect to the point of attachment of a substituent.

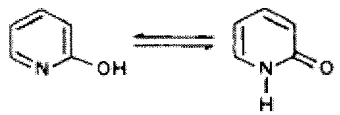
*Examples.* 1-Chloropropane ($ClCH_2CH_2CH_3$) and 2-chloropropane ($CH_3CHClCH_3$).

**5.060 Tautomers**
Structural isomers of different energies which are interconvertible via a low energy barrier; the isomerization involves atom or group migration.

**5.070 Proton Tautomers (Prototropic Tautomers)**
Structural isomers of differing energies that interconvert via migration of a proton; most commonly they have the general structures:

$$H{-}A{-}B{=}Y \rightleftharpoons A{=}B{-}Y{-}H$$

*Examples.* Enol-keto isomerization (Sect. 4.190) is an example of prototropy (change in position of a proton). The interconversion of the tautomers 2-hydroxypyridine, Fig. 5.070*a*, and pyridone, Fig. 5.070*b*.




(*a*) (*b*)

**Figure 5.070** Prototropic tautomers; (*a*) 2-hydroxypridine and (*b*) 2-pyridone.

**5.080 Valence Tautomers**
Structural isomers or degenerate species (see Sect. 5.090) that are interconvertible by reorganization of some of the bonding electrons. The interconversion is accompanied by atom movement but does not involve atom migration. (In this sense valence tautomers are not actually tautomers and therefore should preferably be called valence isomers.) Valence tautomers can be separately identifiable molecules or if they have the same structure (degenerate species) the individual atoms can be separately identified. Valence tautomers should not be confused